Pulmonary Complications in Adult Blood and Marrow Transplant Recipients*

Autopsy Findings

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Study objective: **To describe the pulmonary findings at autopsy of blood and bone marrow transplant (BMT) recipients.**
Design: **Retrospective.**
Setting: **An academic medical center.**
Patients: **Seventy-one deceased adult BMT recipients.**
Interventions: **None.**
Measurements: **Antemortem and postmortem pulmonary findings.**
Results: **The transplants were allogeneic in 39 patients (55%), with a peripheral stem cell source in 43 patients (61%). Death occurred at a median of 1.30 months after transplant. Ninety-six pulmonary complications were noted in 63 patients (89%): 27 infectious (bacterial bronchopneumonia, n = 13; pulmonary aspergillosis, n = 11; cytomegalovirus pneumonia, n = 2; and Candida bronchopneumonia, n = 1) and 69 noninfectious (diffuse alveolar damage, n = 35; diffuse alveolar hemorrhage [DAH], n = 10; amyloidosis, n = 9; pulmonary embolism, n = 5; lymphoma/leukemia, n = 4; bronchiolitis obliterans, n = 2; bronchiolitis obliterans organizing pneumonia, n = 1; pulmonary alveolar proteinosis, n = 1; aspiration pneumonia, n = 1; and acute and organizing pneumonia, n = 1). Twenty-seven of the 96 complications (28%) were diagnosed antemortem. Infectious complications were more likely to be diagnosed antemortem compared to noninfectious complications (48% vs 20%, p = 0.006). Six of the 13 patients with bronchopneumonia (46%), 5 of the 11 patients with pulmonary aspergillosis (45%), and 7 of the 8 patients with DAH (88%) at autopsy were not receiving treatment for these conditions at the time of death. Ten patients being treated for suspected pulmonary aspergillosis, 7 patients treated for suspected pulmonary cytomegalovirus infection, 22 patients treated for suspected bacterial pneumonia, 2 patients treated for suspected *Pneumocystis carinii* pneumonia, and 12 patients treated for DAH at the time of death had no evidence of these conditions at autopsy. The most common immediate cause of death was respiratory failure (n = 37, 52%).**
Conclusions: **Pulmonary complications, the majority not diagnosed antemortem, are the most common cause of death in BMT recipients. As the result of underdiagnosis, BMT recipients may not receive appropriate therapy for potentially treatable pulmonary complications.**
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Key words: aspergillosis; autopsy; bone marrow transplantation; bronchiolitis obliterans; bronchiolitis obliterans organizing pneumonia; cause of death; pneumonia

Abbreviations: BMT = blood and bone marrow transplant; BO = bronchitis obliterans; BOOP = bronchiolitis obliterans organizing pneumonia; DAD = diffuse alveolar damage; DAH = diffuse alveolar hemorrhage; IQR = interquartile range; PCP = *Pneumocystis carinii* pneumonia

Tens of thousands of patients receive blood and bone marrow transplants (BMTs) annually to treat otherwise potentially fatal diseases.[1] Earlier publications[2,3] have suggested that pulmonary complications occur in approximately 30 to 60% of BMT recipients. Because of the absence of graft-vs-host disease and the infrequent use of immunosuppressant medications and radiation therapy, pulmonary complications are less common in autologous compared to allogeneic BMT recipients.[4–6] The spectrum of pulmonary complications in BMT recipients might be expected to change with advances in supportive care, increased application of BMT for older patients, widespread application of prophylactic antibiotics, and newer antiviral and antifungal agents.[1,7,8]

Both infectious and noninfectious findings are frequently found at autopsy of BMT recipients.[9–12] In a 1995 report,[13] one or more infectious complications were identified in the majority of 56 BMT recipients at autopsy, and most of the nonbacterial infections were not identified antemortem. Despite the availability of effective prophylaxis, *Pneumocystis carinii* pneumonia (PCP) has been identified in approximately 18% of immunocompromised patients without AIDS, including BMT recipients.[14,15] Noninfectious pulmonary complications also develop commonly in BMT recipients.[16] In an autopsy study[12] of umbilical cord blood transplant recipients, diffuse alveolar damage (DAD) was found in approximately one half of the patients. Idiopathic pneumonia syndrome, bronchiolitis obliterans (BO), and pulmonary veno-occlusive disease are among the noninfectious pulmonary complications that have been diagnosed at autopsy in a significant number of BMT recipients.[17–19]

While a significant concordance was noted between premortem clinical diagnosis and postmortem findings in a study[9] of 28 critically ill BMT recipients, minimal data are available on the correlation of autopsy findings and antemortem clinical suspicion, diagnosis, and treatment of pulmonary complications. Most of the previous studies[9,11–13,19–21] of autopsy in BMT recipients were not focused on pulmonary complications, or included predominantly allogeneic recipients for whom bone marrow was the stem cell source. The purpose of this study was to describe the pulmonary findings at autopsy of BMT recipients during a recent time period, in a population including both autologous recipients and a peripheral stem cell source.

Materials and Methods

In this retrospective, cohort study, we reviewed the medical and autopsy records of BMT recipients who died at Mayo Medical Center, Rochester, MN. Mayo Medical Center is a tertiary care medical center with two hospitals, Rochester Methodist and Saint Marys, with a total of approximately 1,900 beds. Patients who received autologous or allogeneic BMT and underwent a postmortem autopsy from August 1996 through May 2003 were included in the study. We excluded from the study patients < 18 years old and those who did not authorize their medical records to be reviewed for research. Patients who died at other institutions were also excluded.

Data collected included demographics, reason for BMT, date of transplant, type of BMT (autologous or allogeneic), source of stem cell (bone marrow or peripheral blood), conditioning regimen, clinical premortem diagnoses, postmortem pulmonary findings, and causes of death. We also noted whether the pulmonary findings at autopsy were diagnosed antemortem. Neutropenia was defined as absolute neutrophil count $< 0.5 \times 10^9$/L. Antemortem clinical diagnoses were determined from physician notes, hospital discharge summaries, laboratory studies, radiologic examinations, and pathology reports. For the antemortem clinical diagnosis of the pulmonary complications, we used the objective criteria outlined in their definitions below. Bacterial bronchopneumonia was defined by the presence of new or worsening pulmonary infiltrate on chest radiograph and the growth of a bacterial pathogen from respiratory specimen associated with two of the following: temperature > 38.5°C or < 35°C, leukocyte count $> 10{,}000/\mu$L or $< 3{,}000/\mu$L, purulent sputum, or change in the character of the sputum. PCP was diagnosed by the identification of *P carinii* in stain or direct fluorescent antibody. Candida pneumonia was defined by the histopathologic or cytopathologic demonstration of the fungus in lung tissue. Aspergillus pneumonia was defined by the histopatholgic demonstration of aspergillus or the isolation of aspergillus in respiratory specimen in the presence of a compatible clinical and radiographic pattern. Cytomegalovirus was considered to be pathogenic if it was isolated by cell cultures from a respiratory specimen or when inclusion bodies were present on histopathologic evaluation. Diffuse alveolar hemorrhage (DAH) was defined by the presence of a widespread alveolar injury (as evidenced by multilobar infiltrates, symptoms and signs of pneumonia, abnormal pulmonary physiology with increased alveolar-to-arterial oxygen gradient); cytologic, pathologic, microbiologic, or virologic studies excluding infection compatible with the diagnosis; and BAL fluid returns becoming progressively bloodier or showing iron-laden macrophages $\geq 20\%$.[22] BO was defined by the presence of obstructive airways with suspected bronchiolitis due to chronic graft-vs-host disease or the demonstration of new-onset airflow obstruction in a BMT recipient without pulmonary symptoms.[16] Bronchiolitis is suspected by the presence of cough, wheezing, dyspnea, or hypoxemia with normal chest radiograph findings. Acute lung injury and ARDS were defined by the criteria of the North American/European consensus conference.[23] We used the 1993 National Heart Lung and Blood Institute workshop summary criteria to define idiopathic pneumonia syndrome.[24]

All autopsies were performed by the Mayo Clinic Department of Pathology. Causes of death were obtained from the death certificates filed by the pathologist and based on autopsy findings. All reports and histologic slides were reviewed. Histologic diagnostic categories included infection as determined by the presence of acute bronchopneumonia, invasive fungal infection, and DAD with identification of organism. DAH was defined by the presence of alveolar hemorrhage involving multiple lobes in the absence of another etiology. If the alveolar hemorrhage did not involve multiple lobes, it was not considered diffuse. Bronchiolitis obliterans organizing pneumonia (BOOP) was diagnosed by the presence of patchy intraluminal fibrosis, consisting of polypoid plugs of immature fibroblasts, resembling granulation tissue embedded in a myxoid matrix.[16] BO was diagnosed when bronchiolar lumen narrowing by concentric fibrous tissue was present. We defined DAD as a pattern of acute lung injury characterized

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